Conte Center Overview

Mapping Neurodevelopmental Abnormality in Schizophrenia

P20 MH62130

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John G. Csernansky, M. D.[1,3]

Deanna Barch, Ph.D.[2]

Randy Buckner, Ph.D.[2]

C. Robert Cloninger, M.D.[1]

Michael I. Miller, Ph. D.[5]

Lynn Selemon, Ph.D.[6]

Paul Thompson, Ph.D.[4]

Departments of [1]Psychiatry, [2]Psychology, [3]Anatomy and Neurobiology, [4]Division of Biostatistics, Washington University School of Medicine

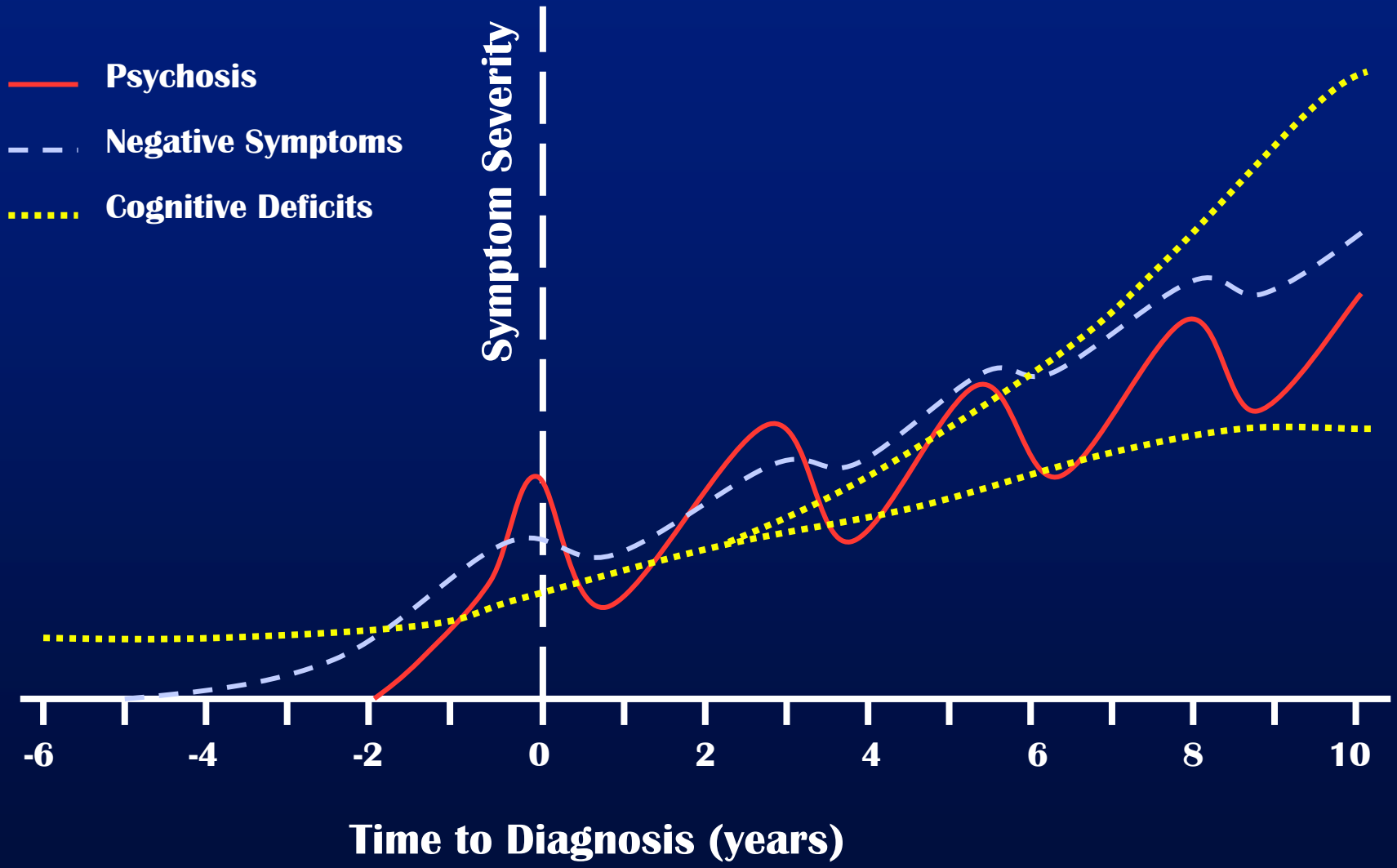
[5]Departments of Biomedical and Electrical and Computer Engineering, Johns Hopkins University

[6]Department of Neurobiology, Yale University

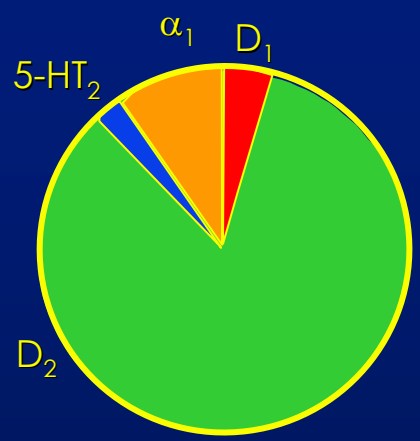
Washington University in St. Louis
School of Medicine

Rationale for the Development of a Multi-Institutional Center to Study the Neurobiology of Schizophrenia

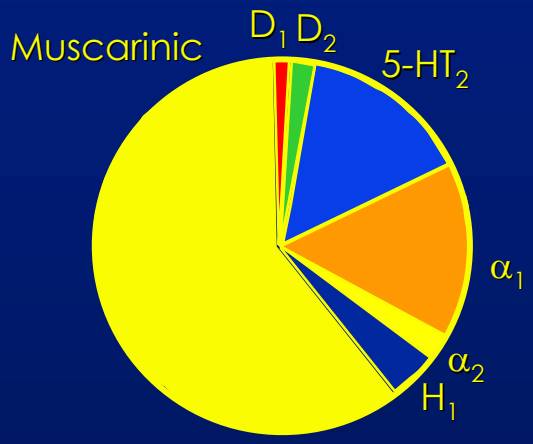
Schizophrenia as a Progressive Illness



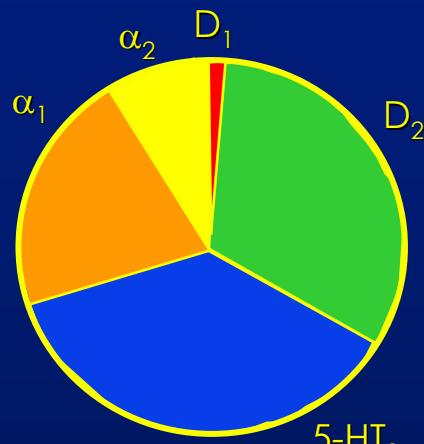
Atypical Antipsychotics: *In Vitro Receptor Profiles*



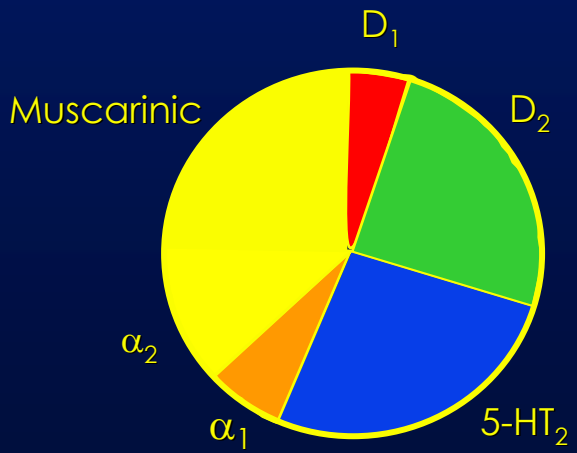
Haloperidol



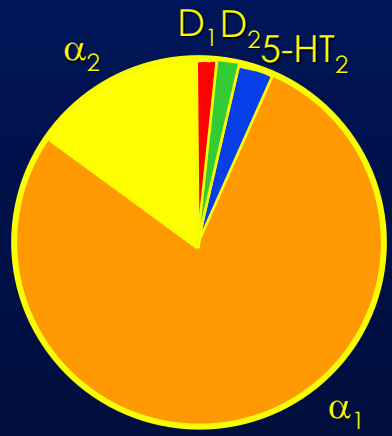
Clozapine



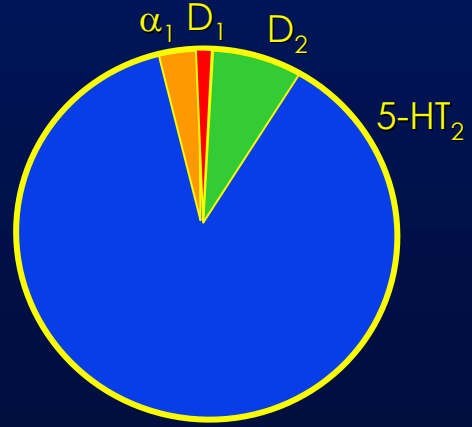
Risperidone



Olanzapine

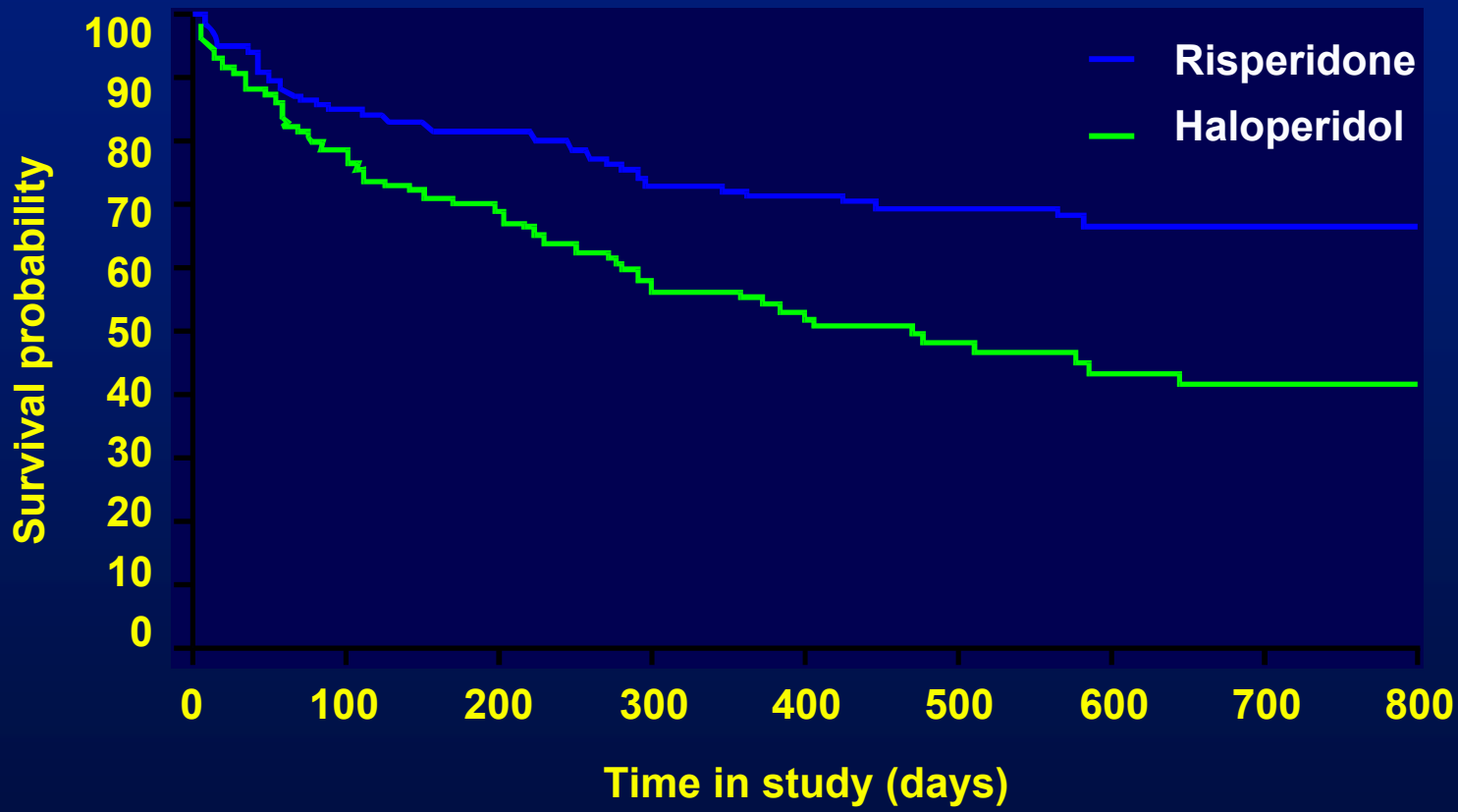


Quetiapine



Ziprasidone

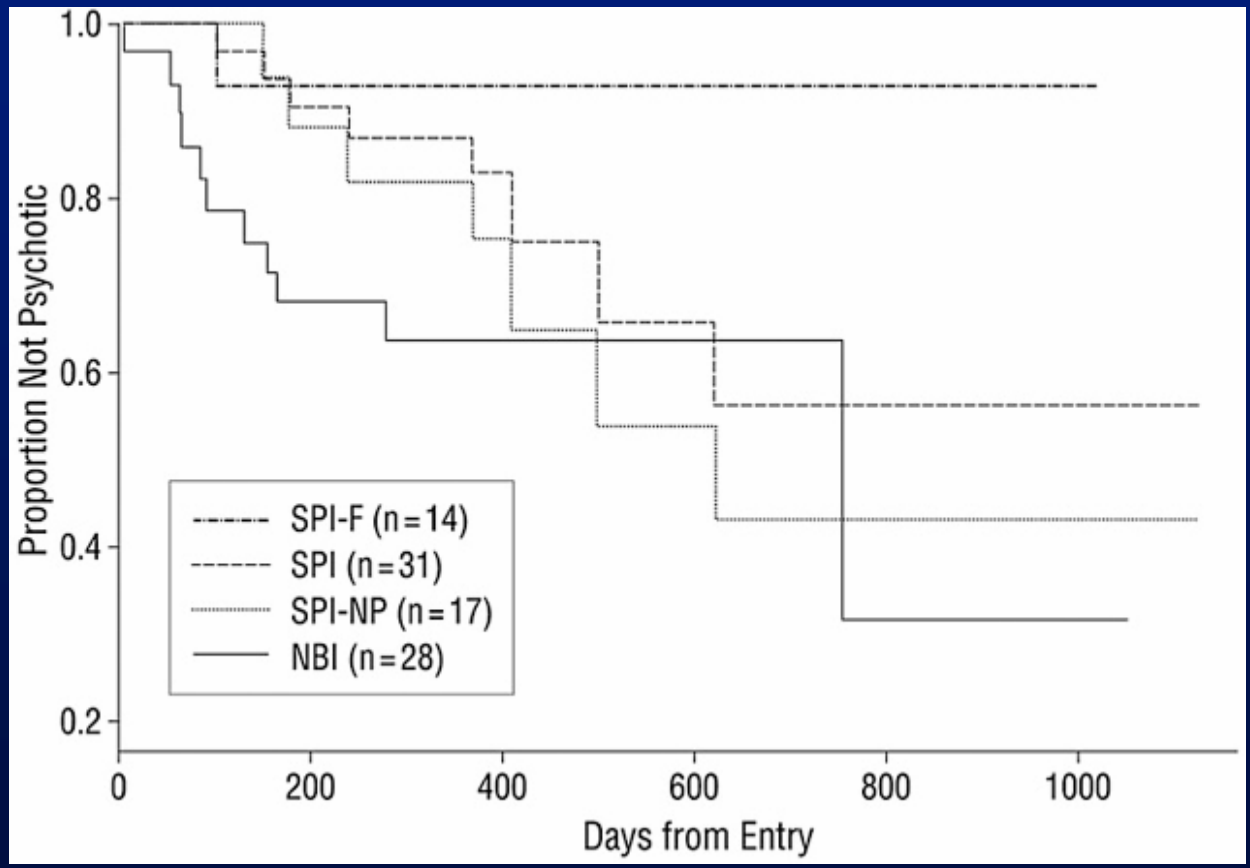
New Drug Treatments May Slow Progression



Mean time to relapse - 452 (risperidone), 391 (haloperidol) days ($p < .001$)

From: Csernansky, et al (2002) New Eng J Med 346:16-22

Can the First Episode of Schizophrenia Be Prevented?



Criteria for Subject Inclusion:

1) schizophrenia in 1st degree relative plus non-specific sxs and function decline

2) attenuated positive symptoms for at least one week, but below psychosis threshold

3) psychotic symptoms above threshold, but lasting less than one week

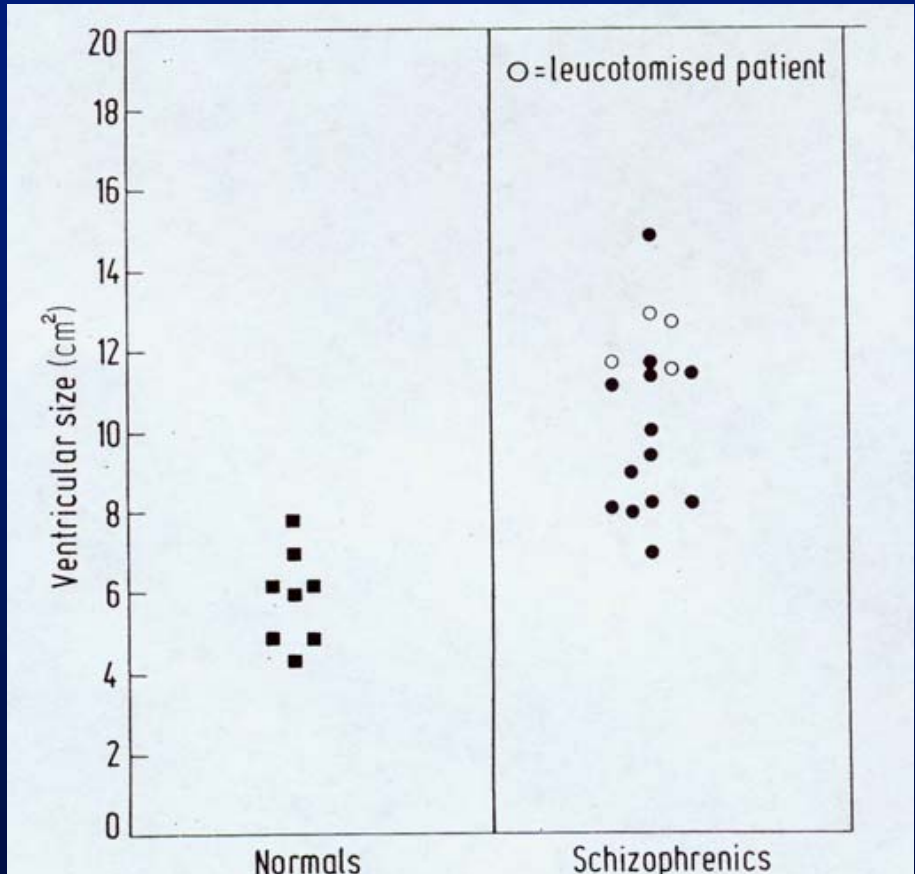
SPI-F - full drug adherence; SPI - poor drug adherence; NBI - needs based intervention

From: McGorry, et al. (2002) Arch Gen Psych 59:921-928.

Surrogate Biomarkers to Improve the Diagnosis of Schizophrenia

- Neurochemistry (dopamine, serotonin, glutamate)
- Genetics (susceptibility genes, modifying genes)
- Cognition (attention, memory, executive function)
- Psychophysiology (SPEM, P50, P300)
- Brain structure (neurodevelopment/neurodegeneration)

Ventricular Enlargement in Schizophrenia is Discovered Using Computerized Tomography



Ventricular size in patients and controls.

Each point represents average of four measurements on photographs.

From: Johnstone, et al (1976) Lancet ii:924-926

Searching for Volume Loss Implicates the Structures of the Limbic System

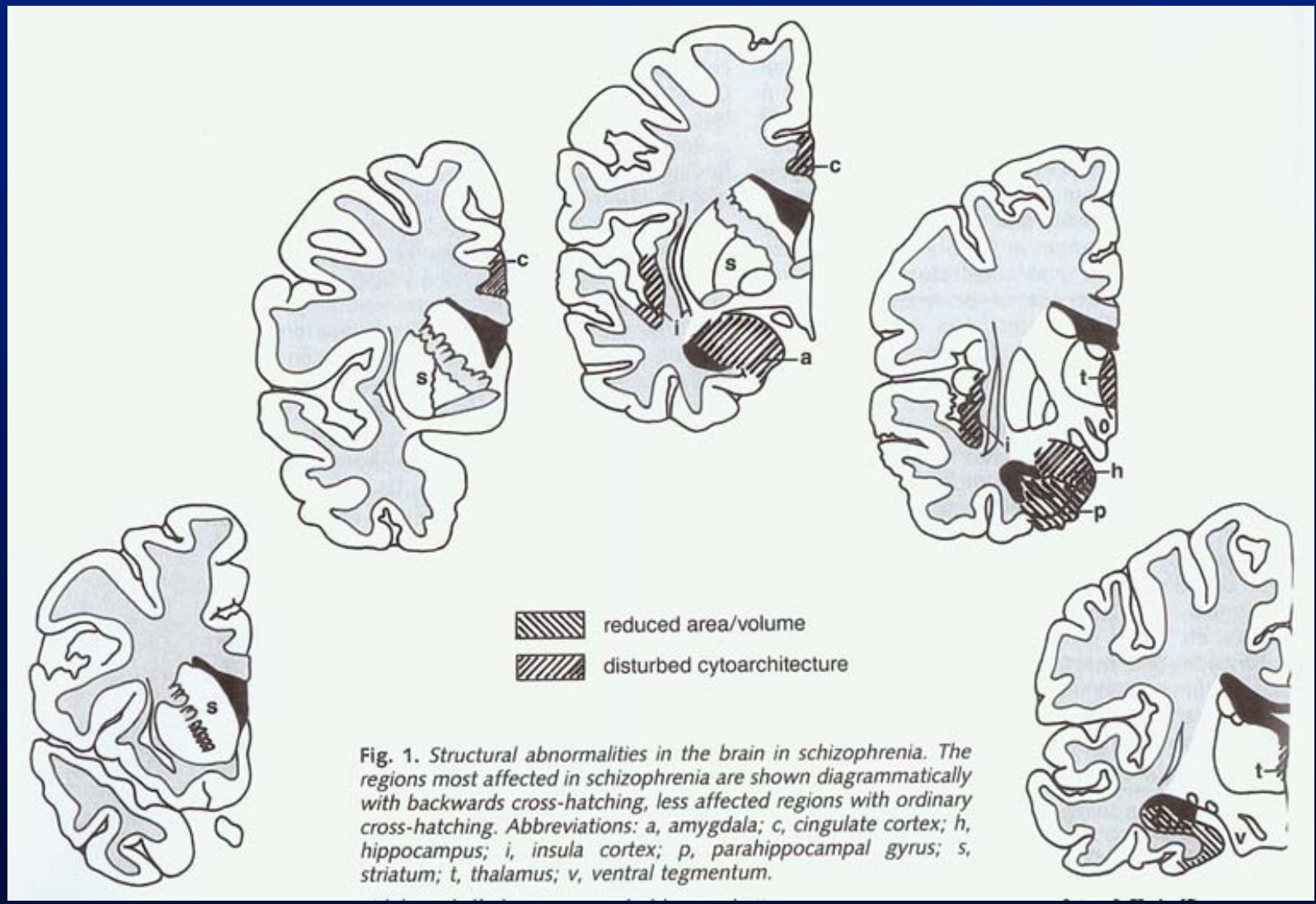
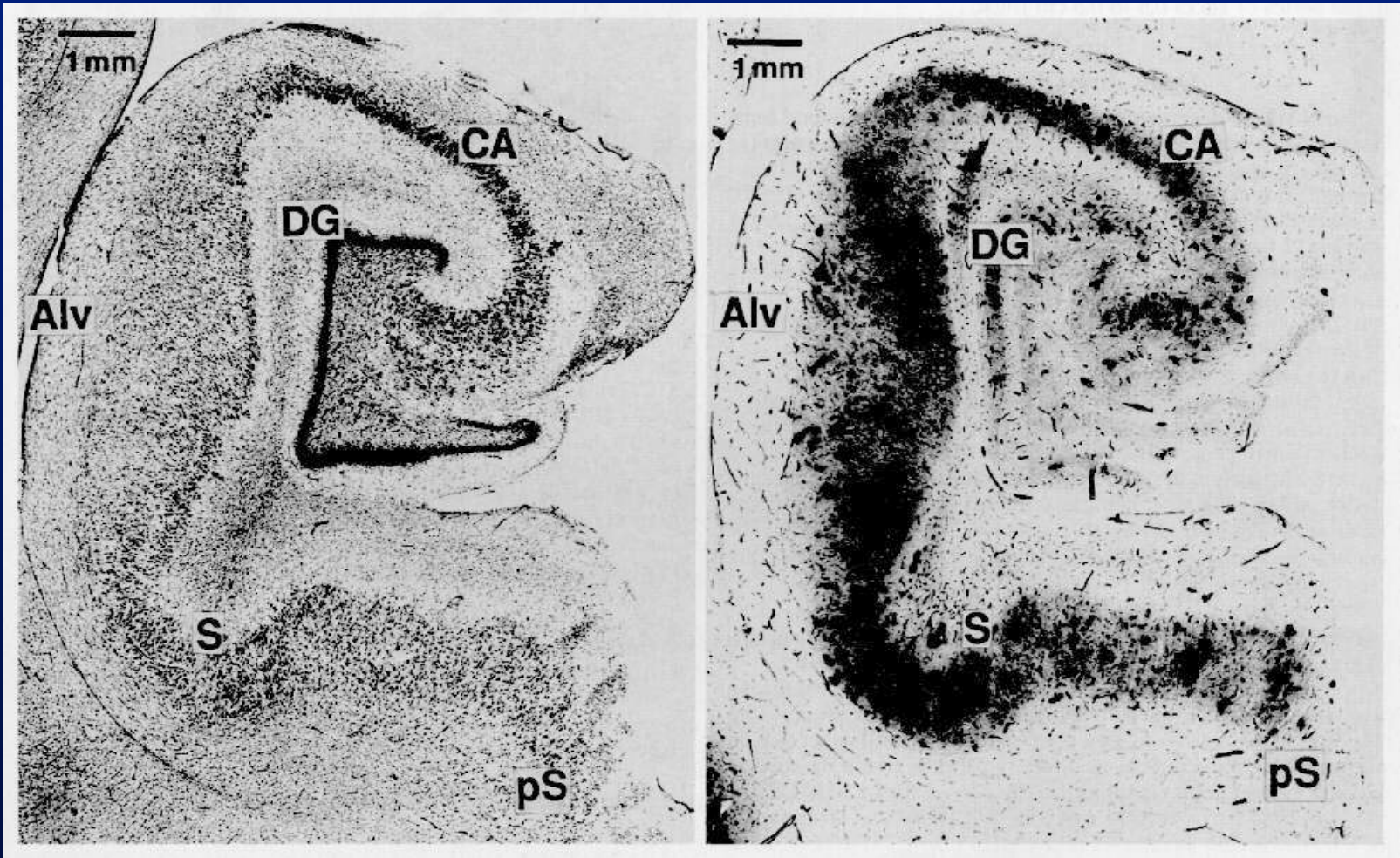


Fig. 1. *Structural abnormalities in the brain in schizophrenia. The regions most affected in schizophrenia are shown diagrammatically with backwards cross-hatching, less affected regions with ordinary cross-hatching. Abbreviations: a, amygdala; c, cingulate cortex; h, hippocampus; i, insula cortex; p, parahippocampal gyrus; s, striatum; t, thalamus; v, ventral tegmentum.*

From: Roberts (1990) TINS 13:207-211

Neuroanatomical Abnormalities Arise from an Early Developmental Defect



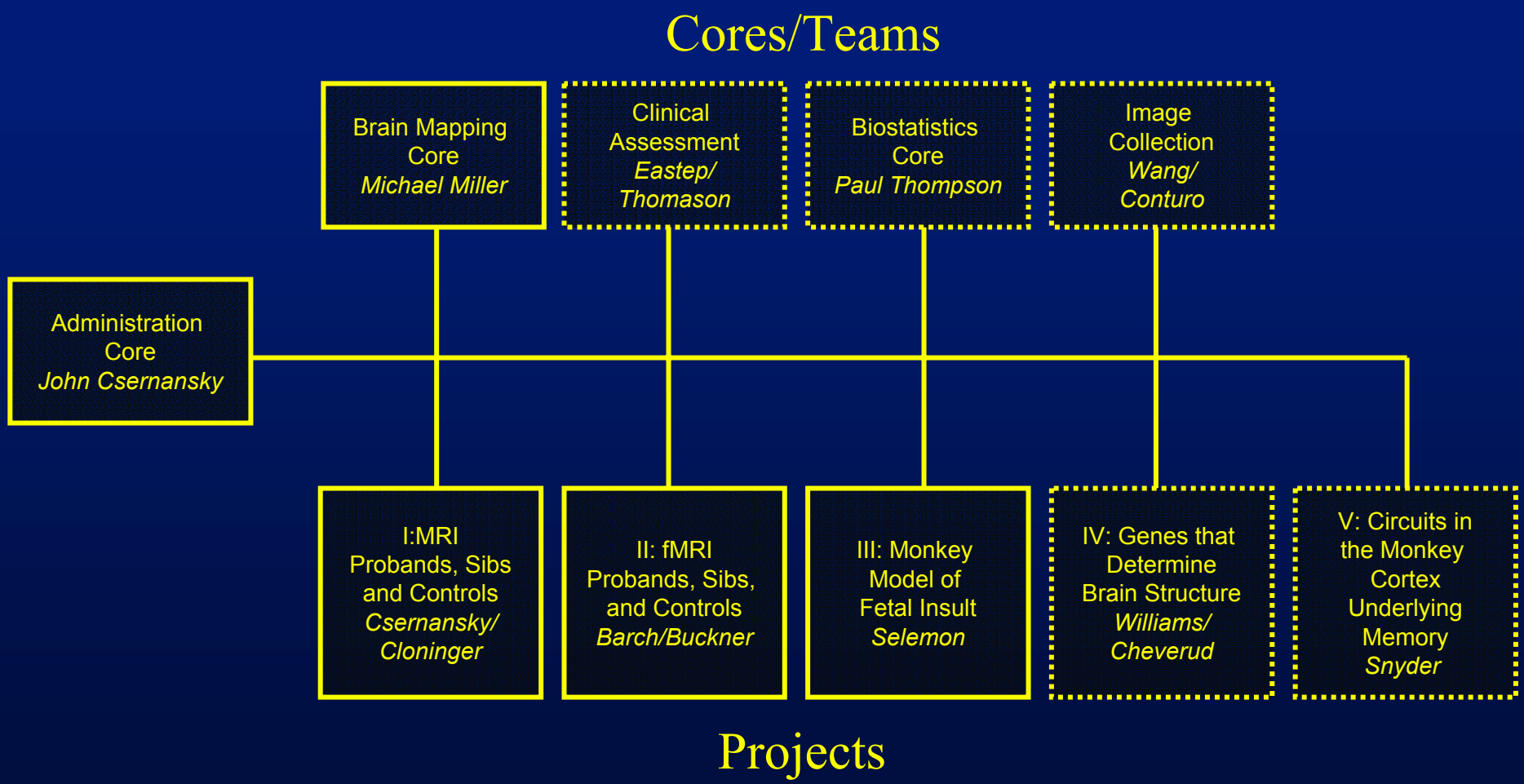
NADPH-d neurons are reduced in gray matter compartments and increased in white matter compartments in the hippocampus of subjects with schizophrenia.

From: Akbarian, et al. (1993) Arch Gen Psychiatry 50:178-187

The Conte Center at Washington University - Central Goals

- define the pattern of neuroanatomical abnormalities in schizophrenia
- investigate their cause(s) (i.e., genetic and environmental)
- explore their cellular basis in an relevant animal model
- establish their cognitive and clinical implications in patients with the disease

The Conte Center at Washington University - Organization



The Conte Center at Washington University - Clinical Assessment Unit

Four subject populations

- Probands with schizophrenia (aged 16-40)
- Siblings of schizophrenia probands (aged 16-26)
- Healthy controls (aged 16-26)
- Siblings of controls (aged 16-26)

Clinical Assessment

- SCID-IV; Semi-structured clinical evaluation
- SAPS, SANS
- MADRS (mood), SUMD (insight)
- SIPS, TCI, Chapman
- Treatment History, ESRS
- Smoking, Alcohol and Drug Use
- Peri-Natal Risk Factors

The Conte Center at Washington University - Clinical Assessment Unit

Cognitive Assessment - Expert Administration

WAIS - vocabulary, matrix reasoning

WMS-III - logical memory, family pictures, digit span, letter/number sequencing, spatial span

Trails A/B, verbal fluency, CVLT-II, Wisconsin Card Sort

Cognitive Assessment - Computerized

CPT - identical pairs, AX, degraded, NBACK

Stroop

Maintenance/manipulation task

Word experiment task

The Conte Center at Washington University - Neuroimaging Protocols

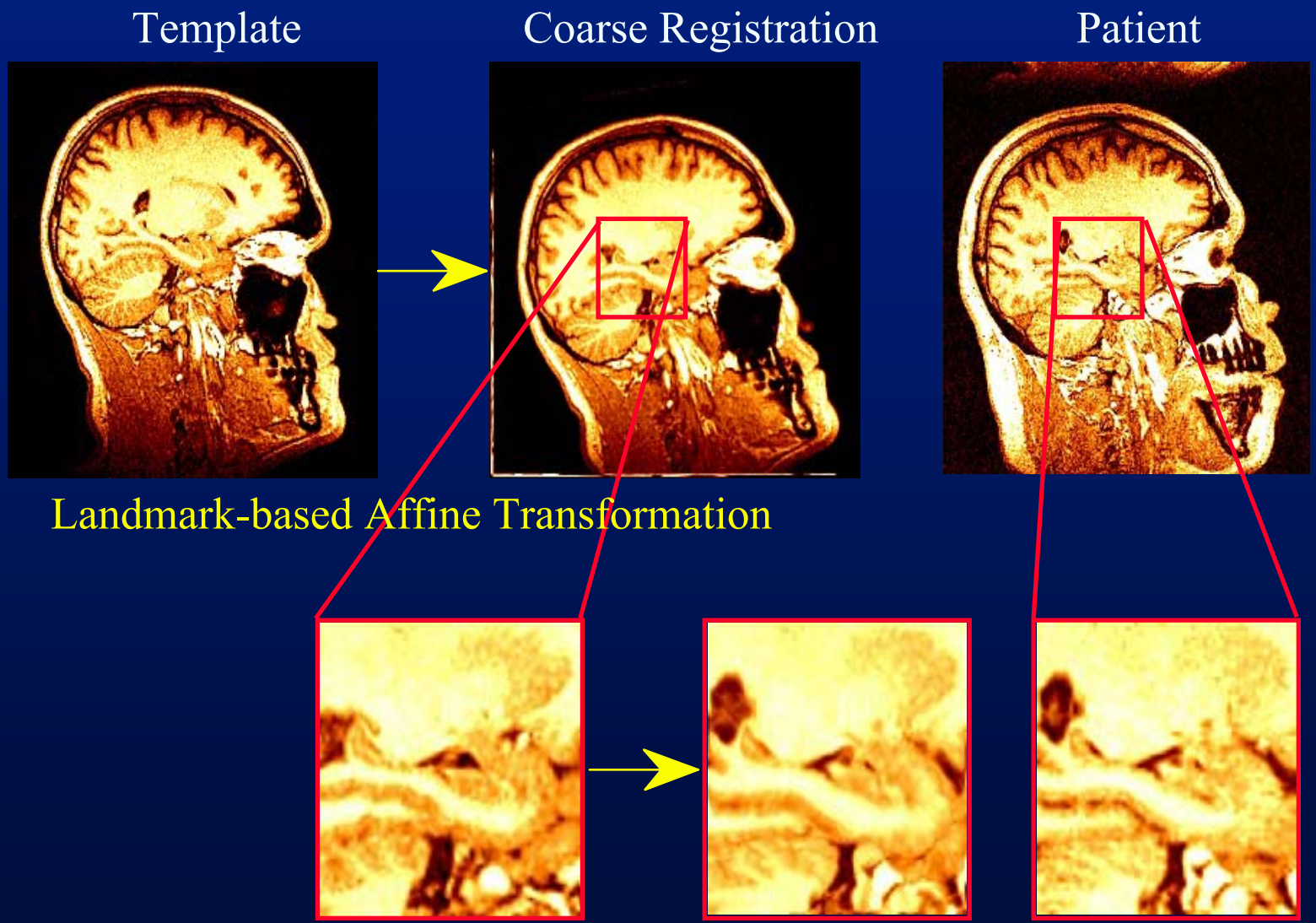
Structural assessment

- MPRAGE x 4
- Turbo-FLASH
- T2-weighted
- DTI
- DTI (high resolution)

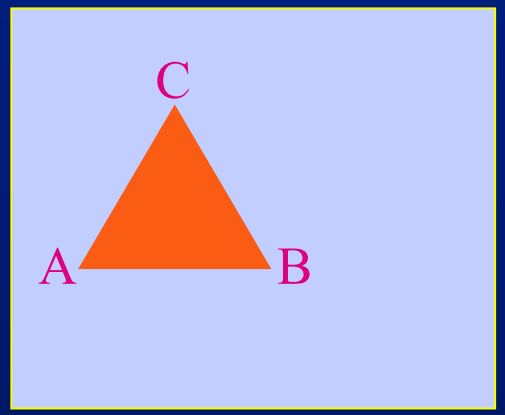
Functional assessment

- Spin-echo, echo-planar, BOLD sensitive
  - 2-BACK, incidental encoding (shallow vs.deep),
    - yes/no recognition
  - Words and Faces

High Dimensional Diffeomorphic Brain Mapping



New Information from Neuroanatomical Shapes



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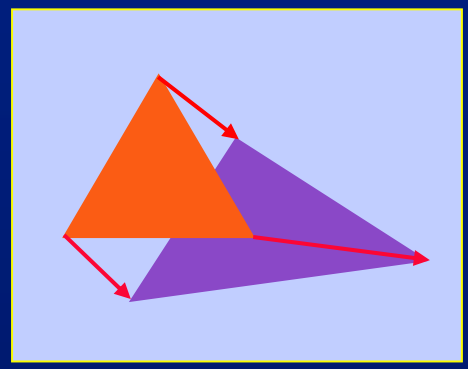

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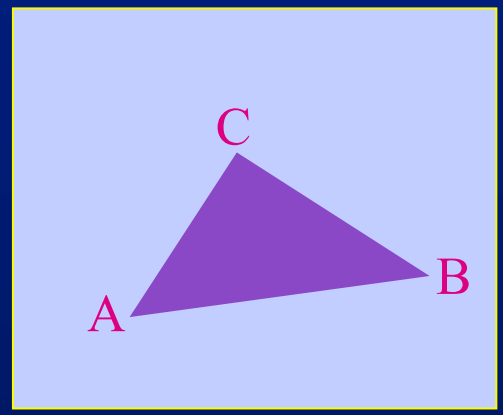

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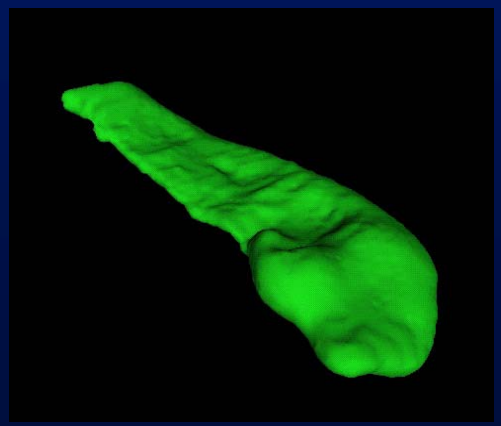

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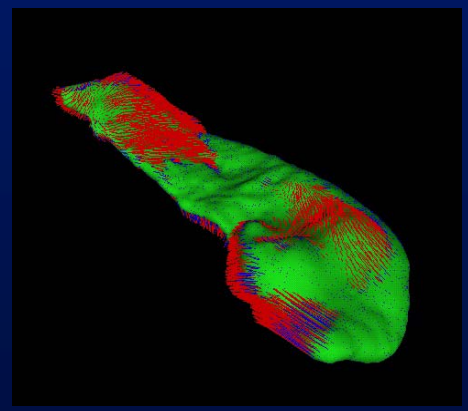

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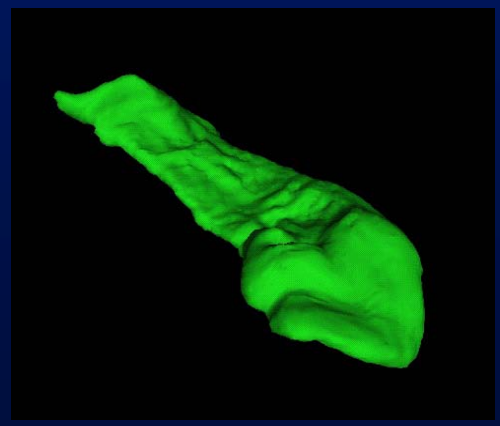

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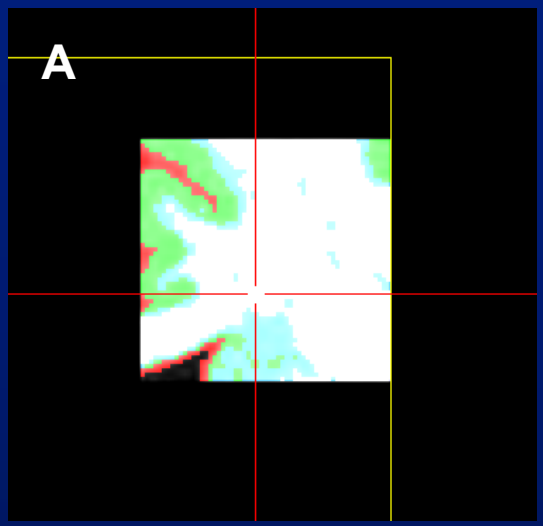
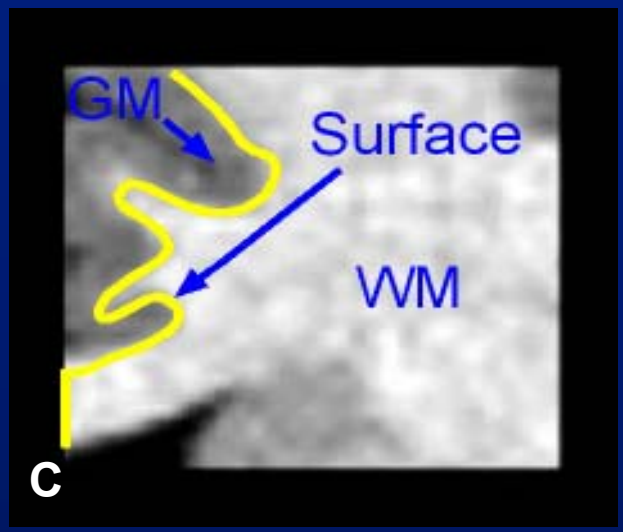
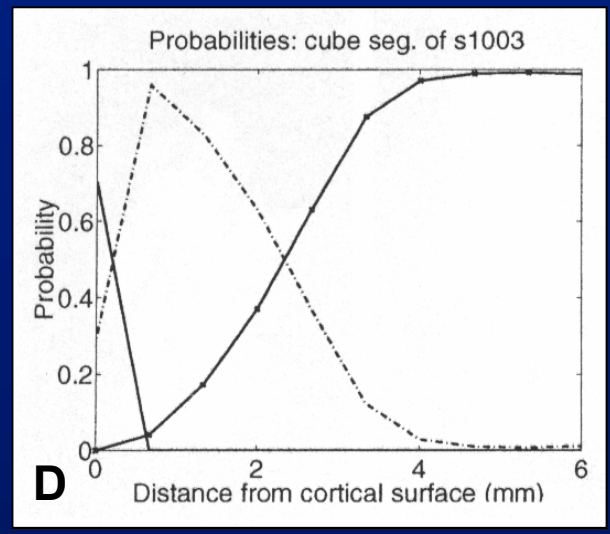
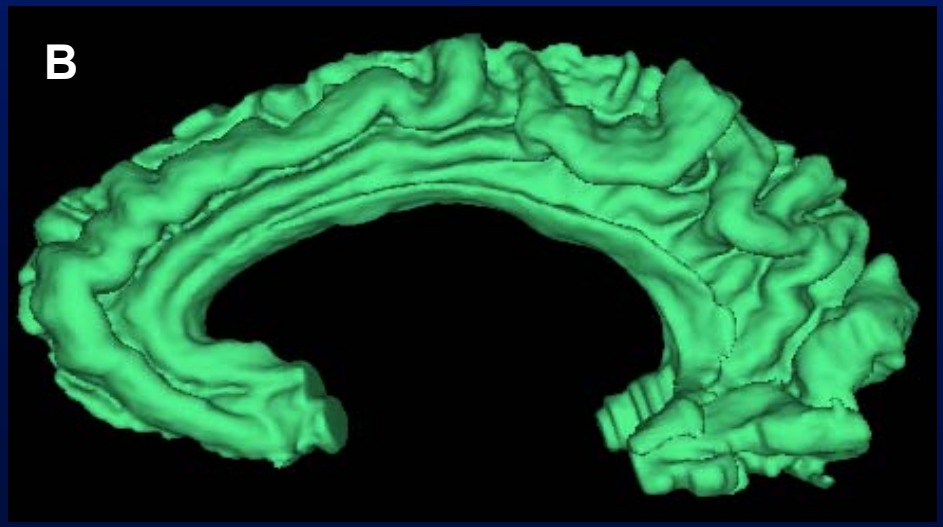
Measuring the Depth of the Cortex









A - Tissue segmentation

B - Identifying the gray/white iso-surface

C- Assessing voxels at varying distances from the gray/white isosurface

D - cumulative probability of gray, white and CSF voxels

From: Miller, et al (2002) submitted for publication

Project 1: Neuromorphometry in Siblings at Risk for Schizophrenia (Csernansky/Cloninger)

Aims:

- Collect high-resolution MR scans in 60 probands with schizophrenia, their younger siblings, and control groups (matched to the siblings)
- Develop a database of neuromorphometric variables for each subject: Volume, shape, symmetry, anisotropy
- Test the hypothesis that the non-psychotic siblings of the schizophrenia probands will demonstrate structural abnormalities intermediate between probands and control groups
- Collection of longitudinal data (anatomical and clinical) so that predictors of later clinical changes can eventually be identified

Detecting Hippocampal Deformities in Schizophrenia: A Replication

Subjects:

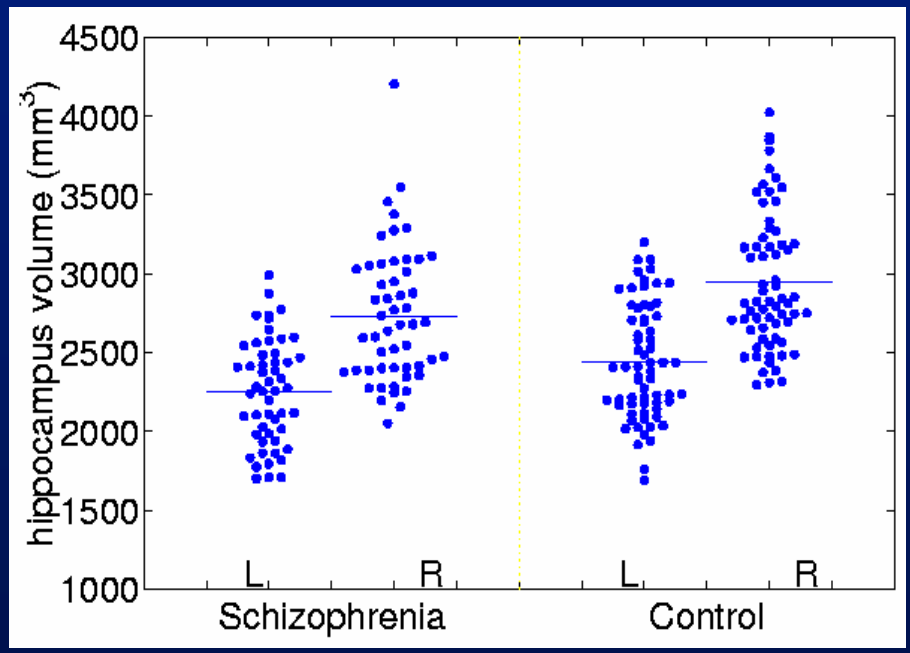
Variables (mean +/- SEM [range])	Schizophrenia Subjects	Healthy Controls
N	52	65
Age	38.0 (1.74 [20-63])	40.0 (1.78 [20-67])
Gender (M/F)	30/22	33/32
Race (Cau/Afr-Amer/Other)	22/30/2	34/18/0
Parental SES	4.1 (0.12 [2-5])	3.6 (0.13 [1.5-5])
Age of Illness Onset	22.8 (1.18 [13-54])	-----
Total SAPS Score	19.7 (2.41 [0-67])	-----
Total SANS Score	19.7 (1.76 [0-52])	-----

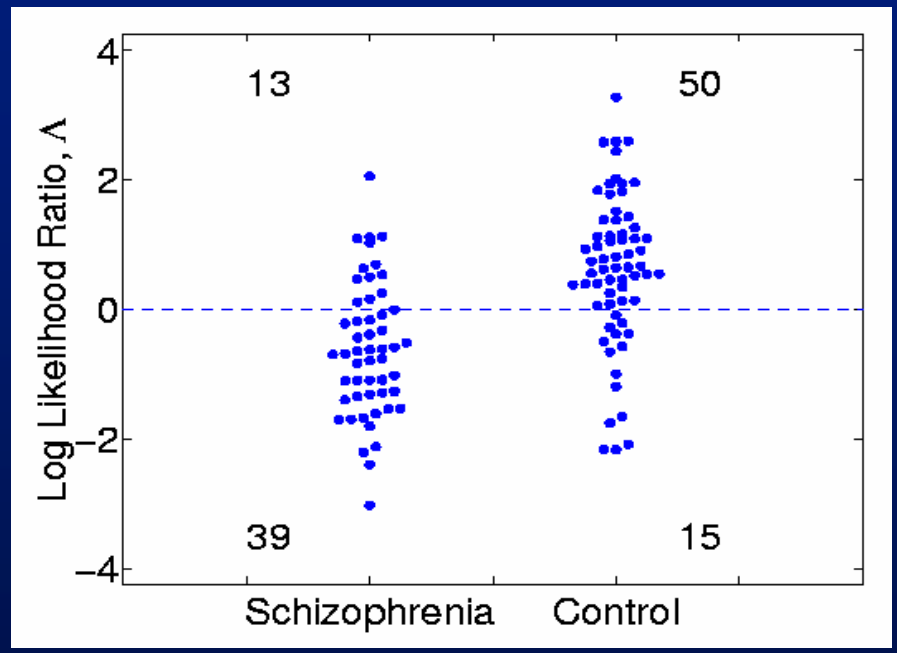
MRI:

Turbo-FLASH sequence at 1 mm x 1 mm x 1 mm resolution

From: Csernansky, et al. (2002) Am J Psychiatry 159:2000-2006.

Comparison of Hippocampal Volumes and Shapes





Volume Scatter Plots

F = 7.9, df = 1,115, p = .006

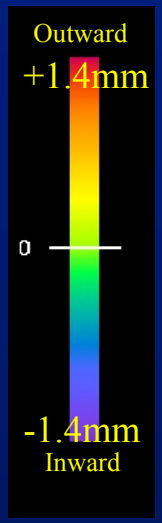
F = 2.5, df = 1,114, p = .12 (covaried for total brain volume)

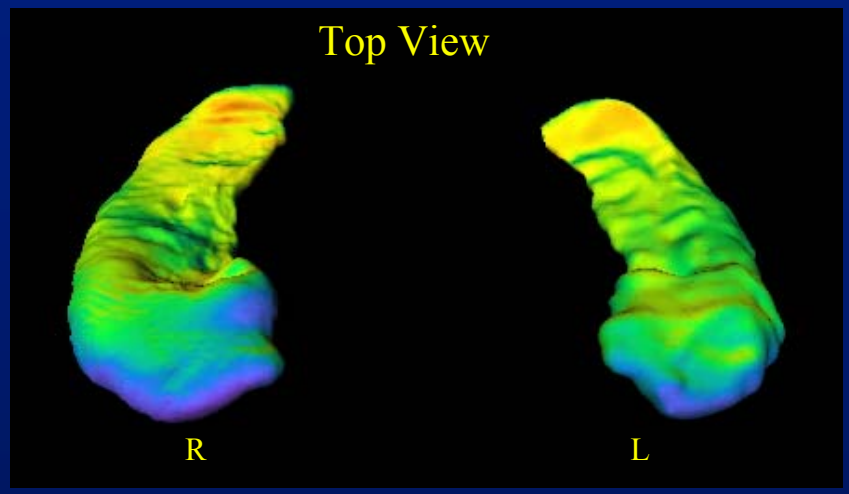
Log-Likelihood Plot

F = 6.9, df = 5,111, p < .0001 (1, 5, 7, 14, 15)

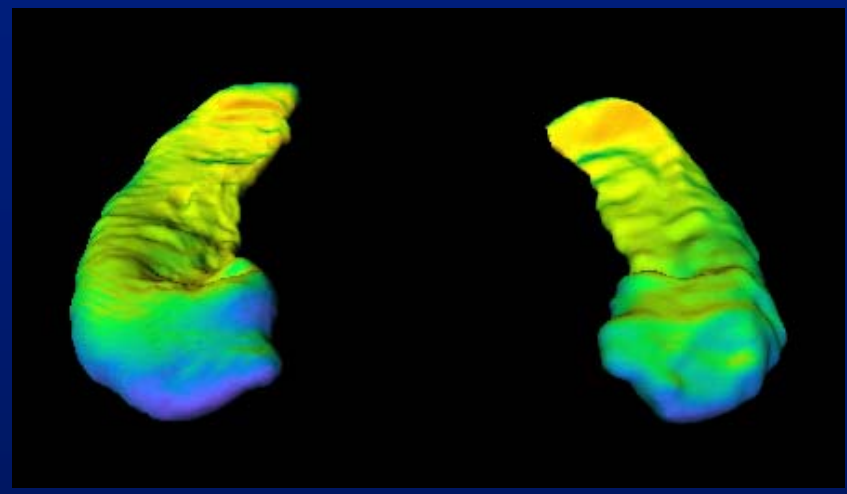
From: Csernansky, et al (2002) Am J Psychiatry 159:2000-2006.

Patterns of Hippocampal Deformity in Schizophrenia

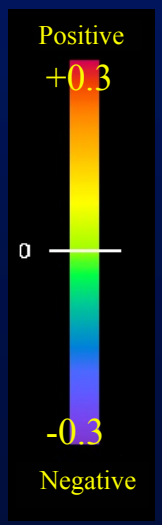


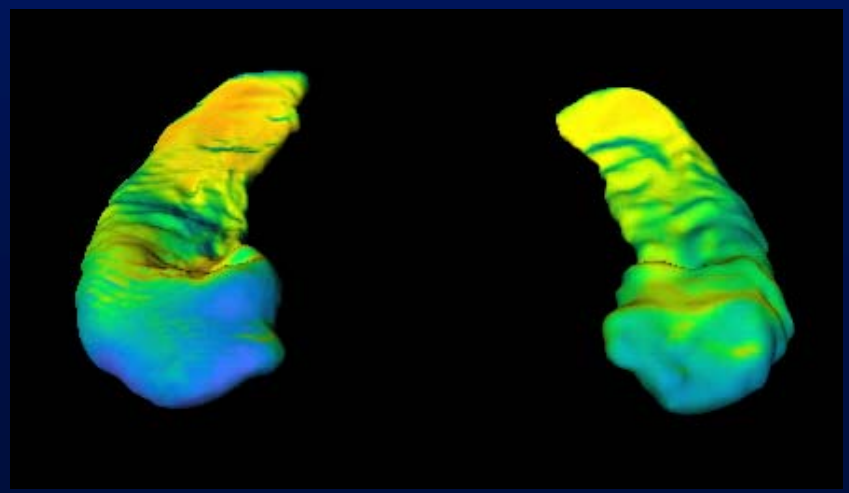


Difference Mapped on Mean Control



Eigenvector Reconstruction



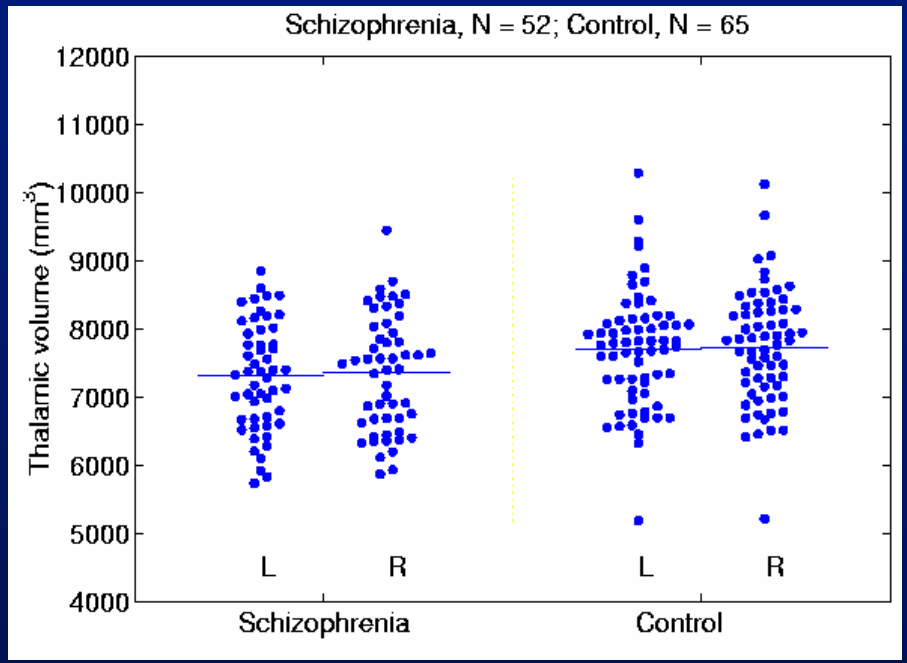


Z-Scores Mapped on Mean Control

Similarity of the patterns of shape deformation demonstrate the physical basis of the eigenvector solution

From: Csernansky, et al (2002)
Am J Psychiatry 159:2000-2006.

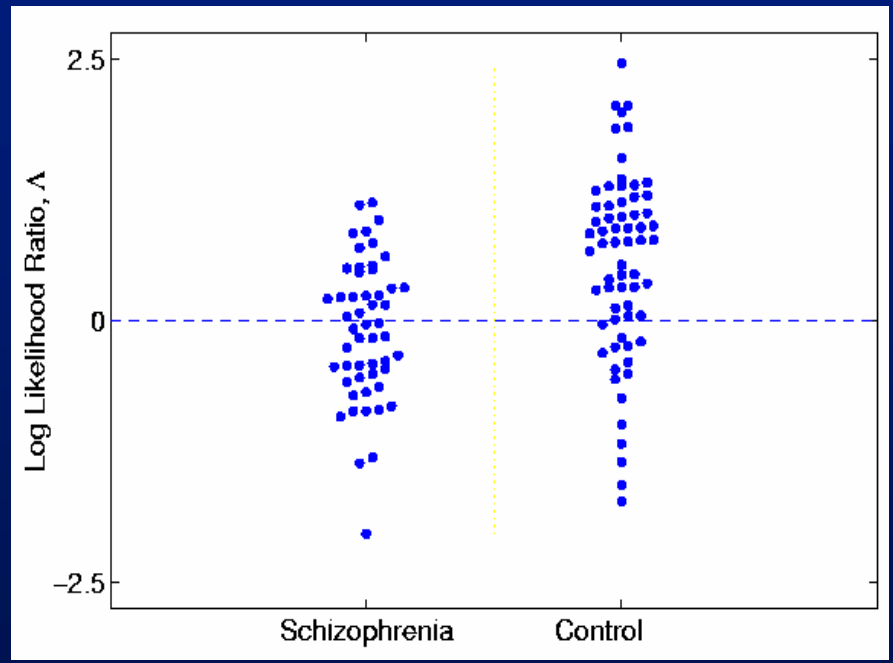
A Study of the Thalamus in Schizophrenia Subjects and Controls



Volume Scatter Plots

F = 6.6, df = 1,115, p = .011

F = 1.3, df = 1,114, p = .26 (covaried for total brain volume)

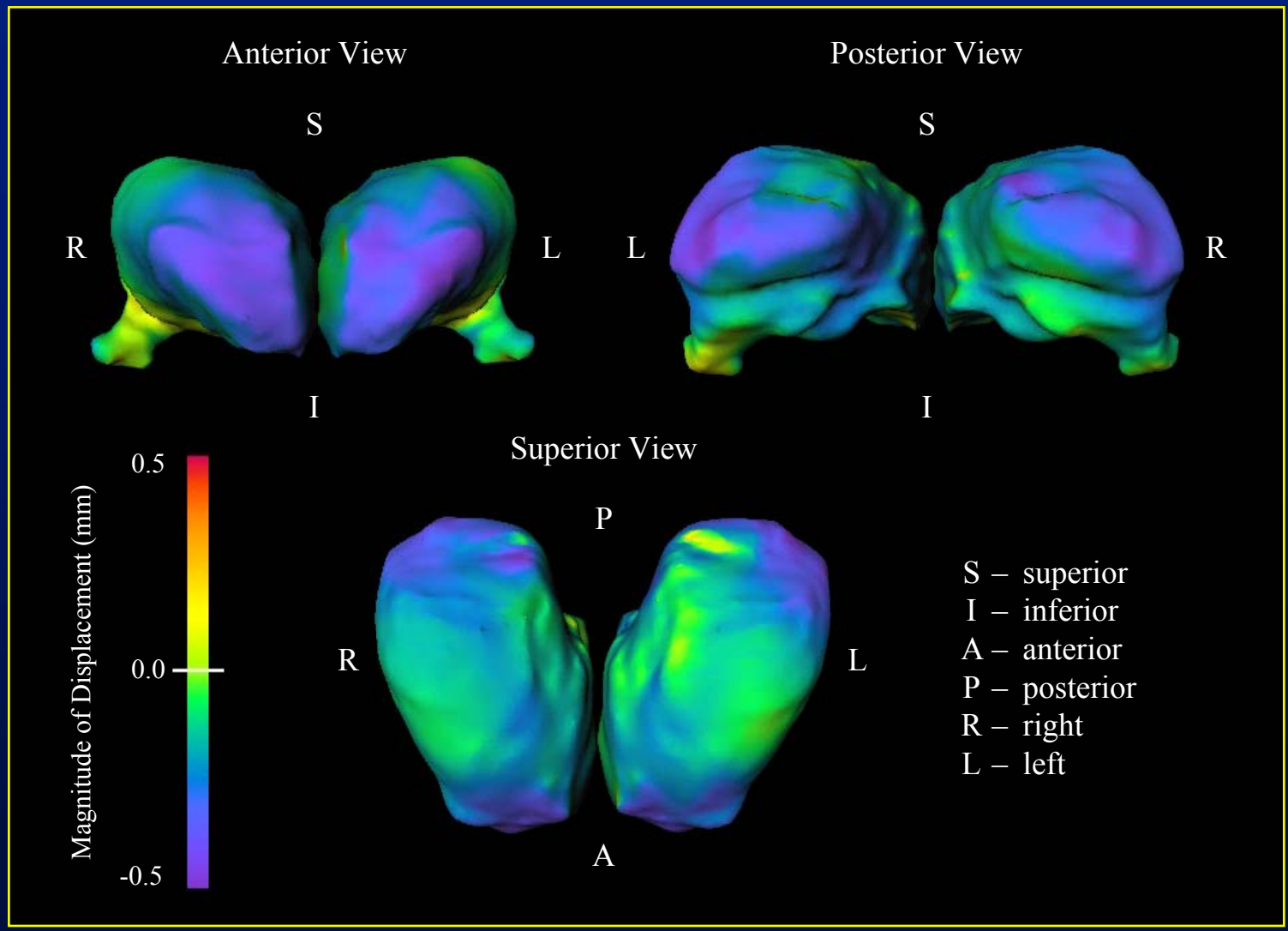


Log-Likelihood Plot

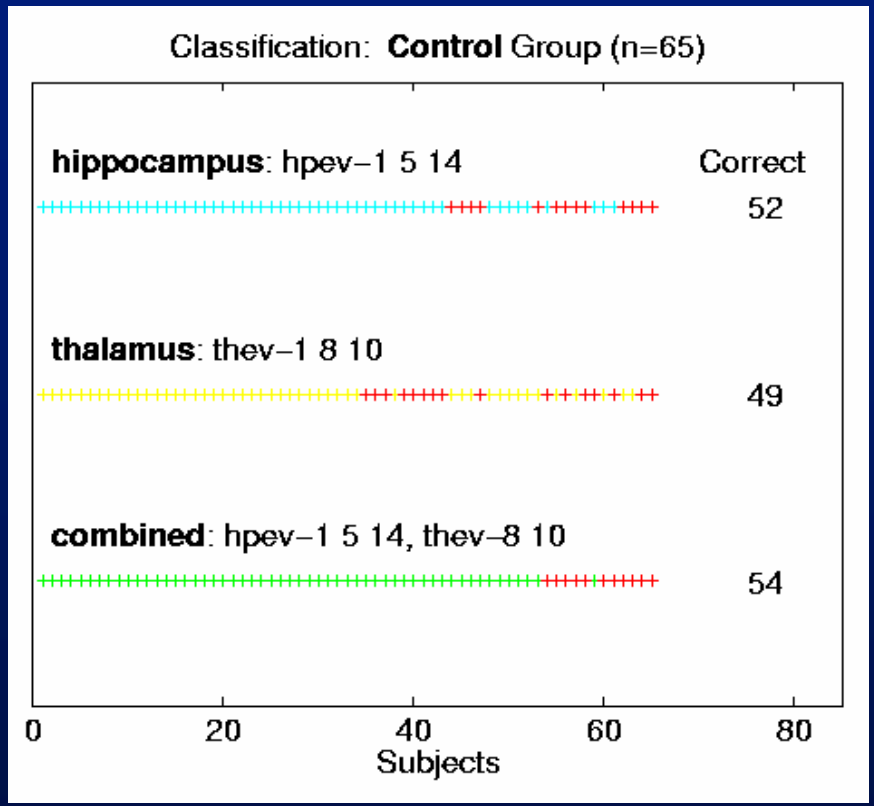
F = 2.8, df = 10,106, p = .004 (first ten EV)

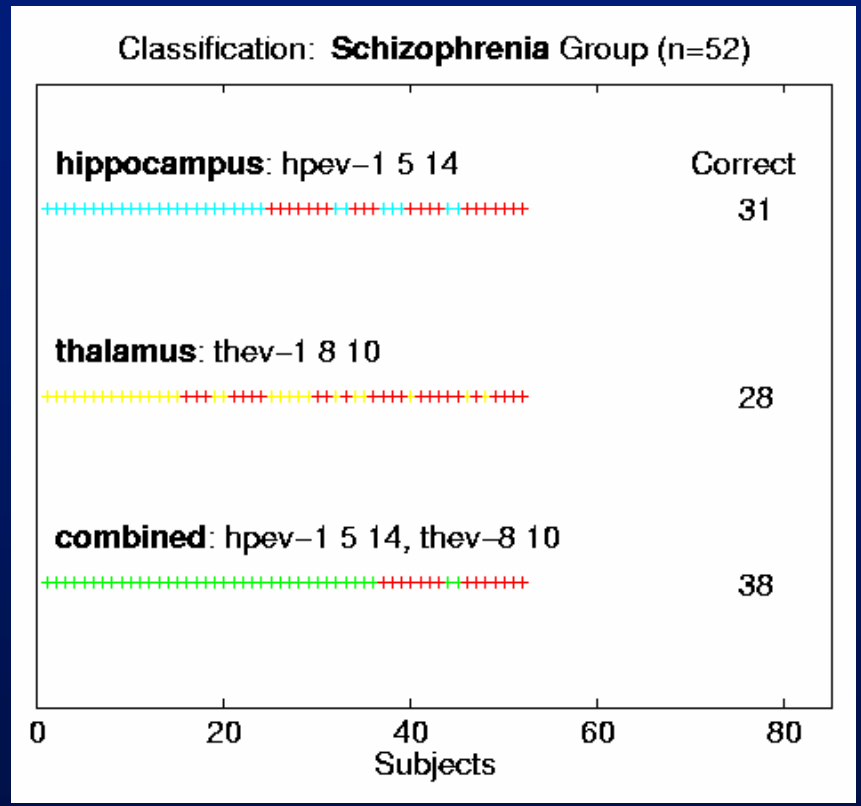
A Study of the Thalamus in Schizophrenia Subjects and Controls

B



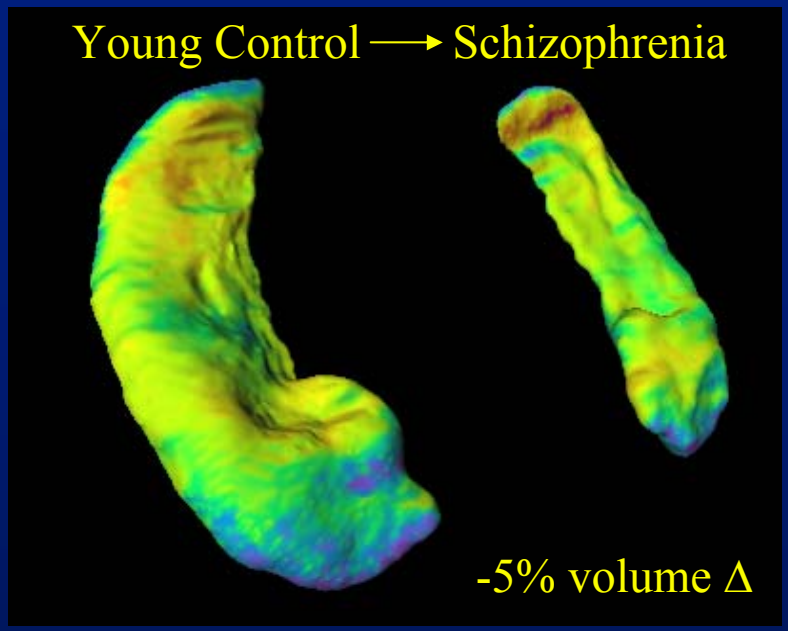
Identifying Schizophrenia Subjects by Combining Brain Structure Shape Information

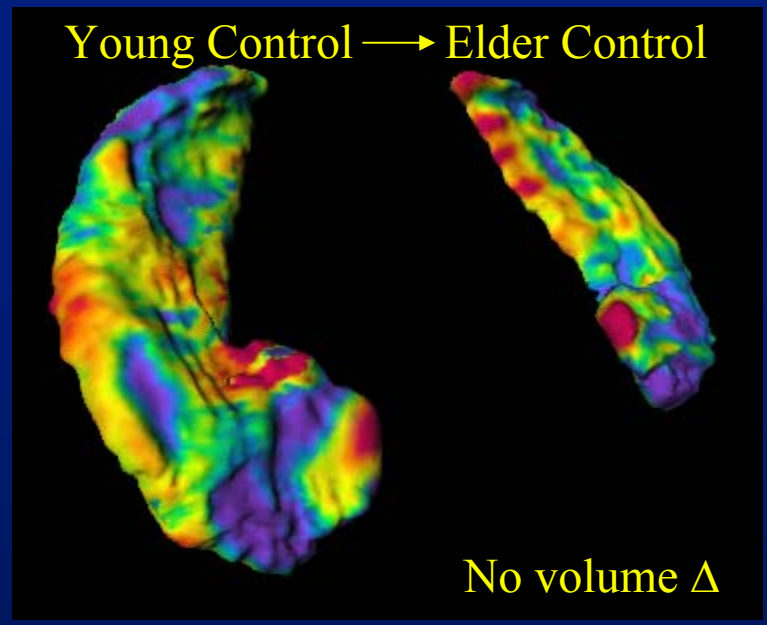


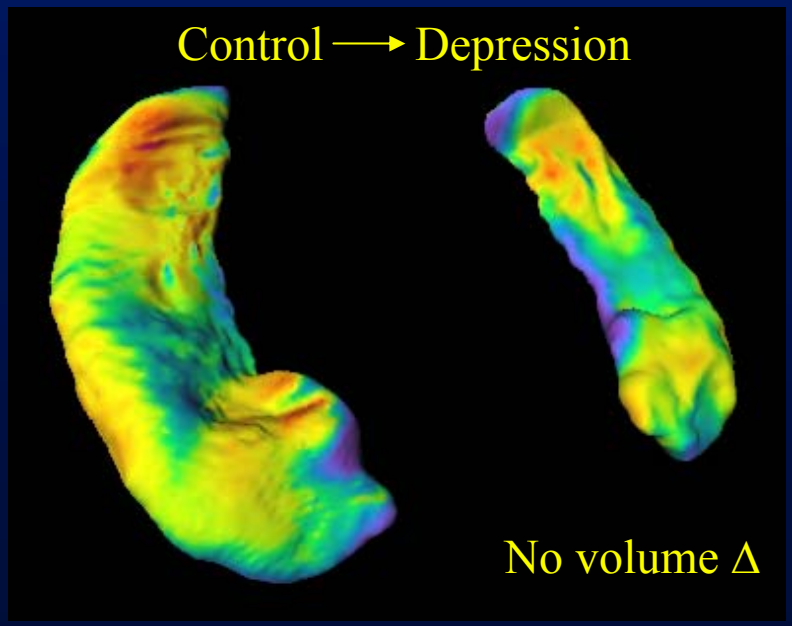


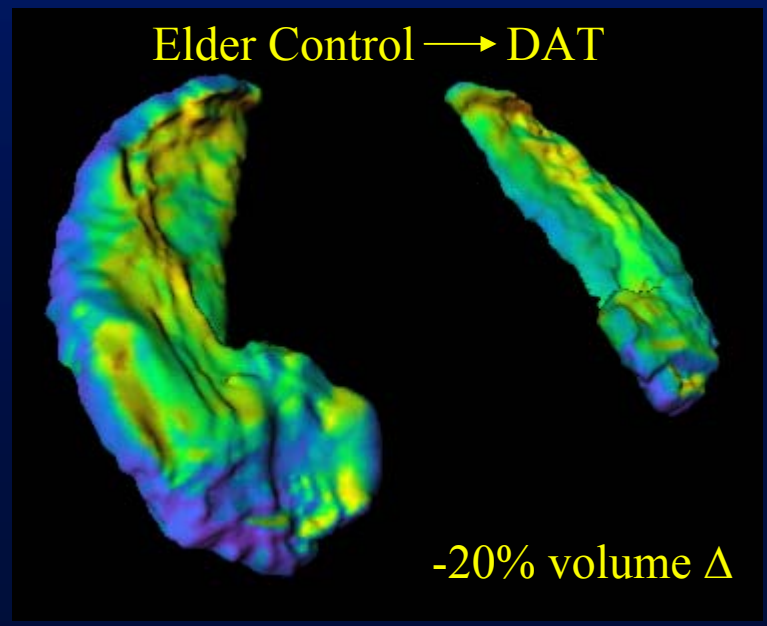
Clues to Explain the Heterogeneity of Schizophrenia ?

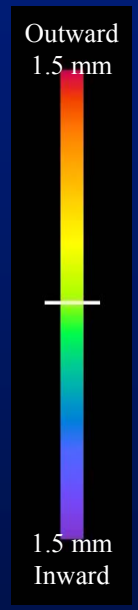
Patterns of Shape Change are Specific











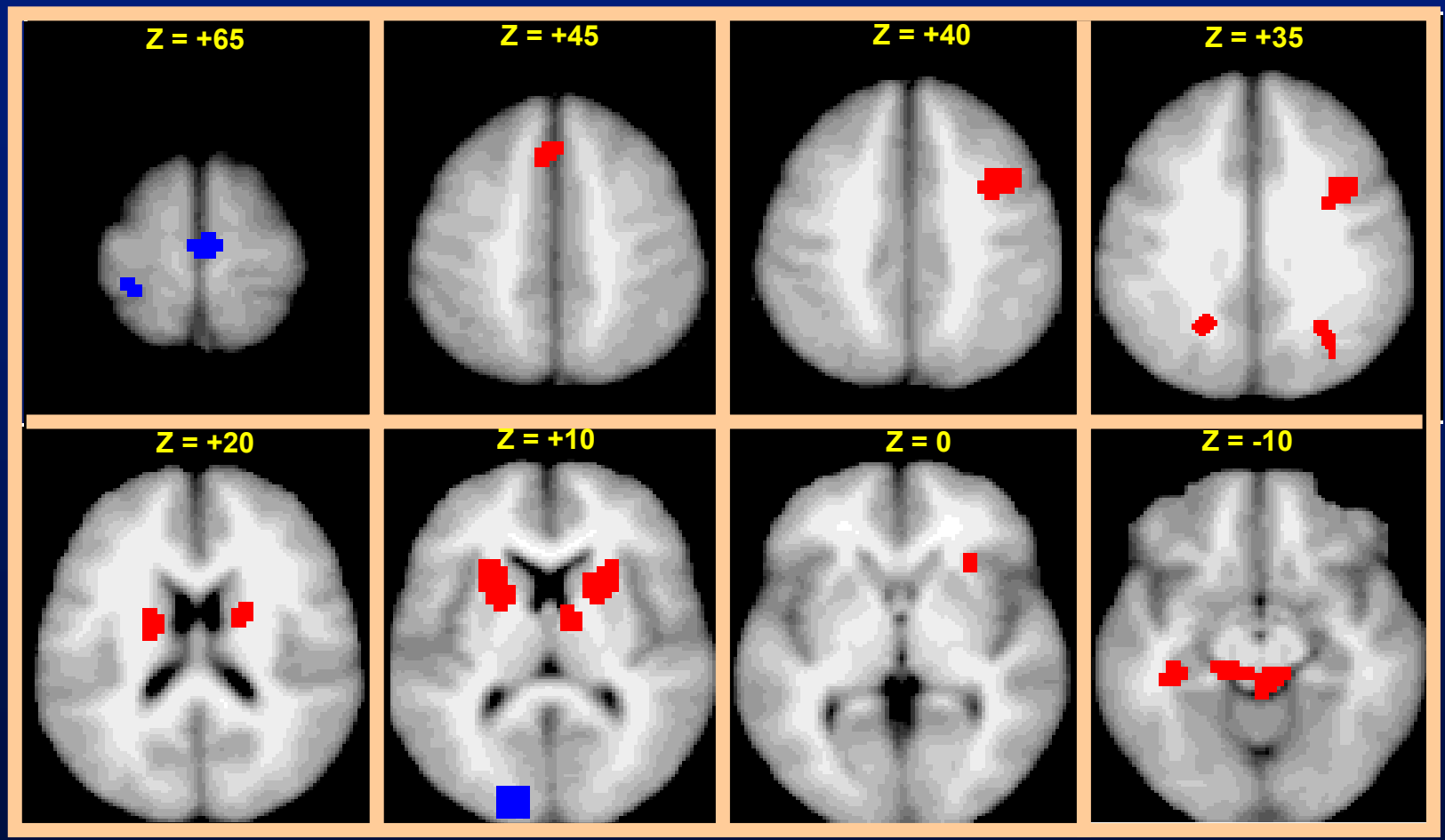
Project 2: Structure, Function and Cognition in Schizophrenia (Barch/Buckner)

Aims:

- Determine the relationships between changes in brain structure and functional activation disturbances during cognitive challenge in subjects with schizophrenia

- Determine the relationships between changes in brain structure and functional activation disturbances during cognitive challenge in the non-psychotic siblings of subjects with schizophrenia

Altered Task-Related Activation in Working Memory and Episodic Memory Tasks



From: Barch, et al (2002) J Abnormal Psychology, 111:478-494.

Project 3: Mapping Abnormal Neurodevelopment in an Animal Model of Schizophrenia (Selemon/Goldman-Rakic)

Aims:

- Collect high-resolution MR images in fetally-irradiated Rhesus monkeys at predetermined developmental time-points
- Evaluate the volume, shape and symmetry of subcortical structures of the monkey brain (e.g., thalamus) that have been directly affected by fetal irradiation
- Evaluate the volume, shape and symmetry of limbic and cortical structures of the monkey brain (e.g.,hippocampus, cingulate gyrus, prefrontal cortex) that may have been indirectly affected by fetal irradiation

Thalamic Deformaties Identified in Fetally-Irradiated Rhesus Monkeys by Diffeomorphic Brain Mapping

Volume Comparisons (mean +/- SD in mm^3)

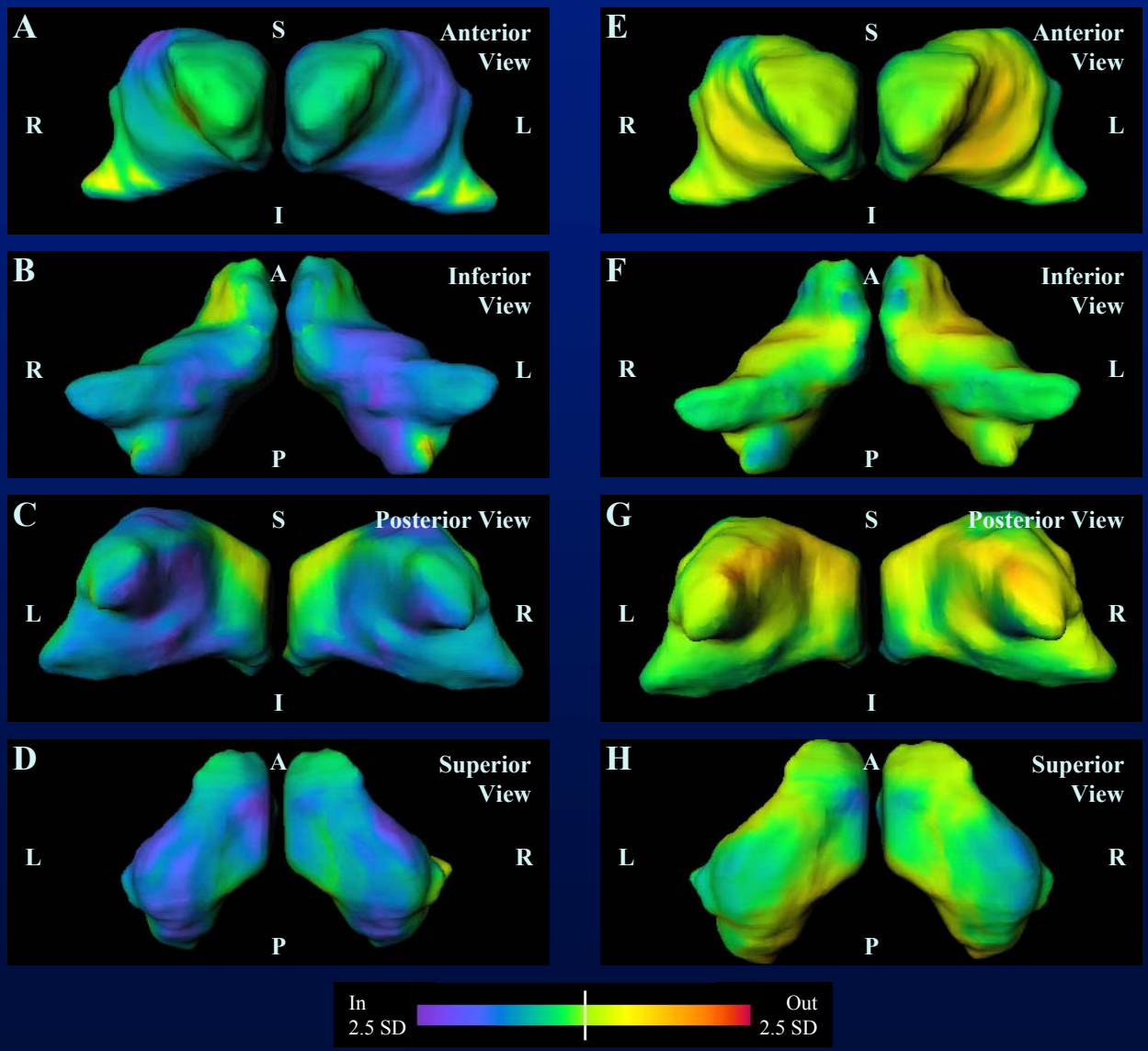
Group (N)	R Thalamus	L Thalamus	Total Cerebrum
EL (3)	416.39 (80.53)	392.24 (79.70)	56574 (9796)
LL (3)	517.48 (69.66)	526.44 (66.63)	55576 (5729)
Control (8)	542.31 (120.17)	537.01 (94.81)	62544 (12178)

Group effect F = 9.48, df = 2,11, p=.005

Early Irradiated < Late Irradiated = Control

From: Schindler, et al (2002) Biol Psychiatry 51:827-837

Thalamic Deformaties Identified in Fetally-Irradiated Rhesus Monkeys by Diffeomorphic Brain Mapping



Eigenvectors 1,4,8,9

EL and Controls - Wilks' Lambda
F= 19.88, p= .003

LL and Controls - non-significant

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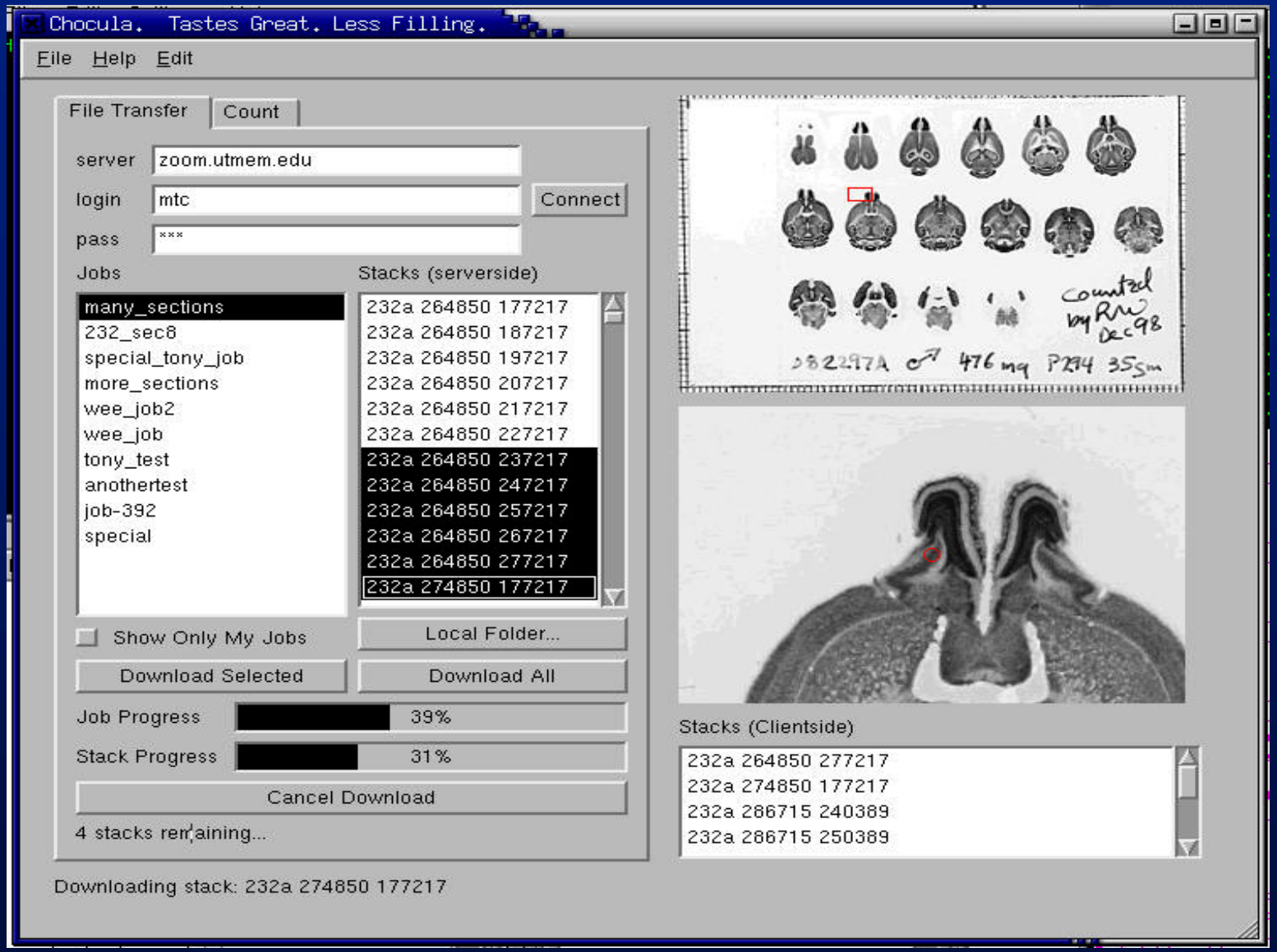
Project 4: Neuroanatomical Trait Loci in Recombinant Inbred Mouse Strains (Williams/Cheverud/Rosen)

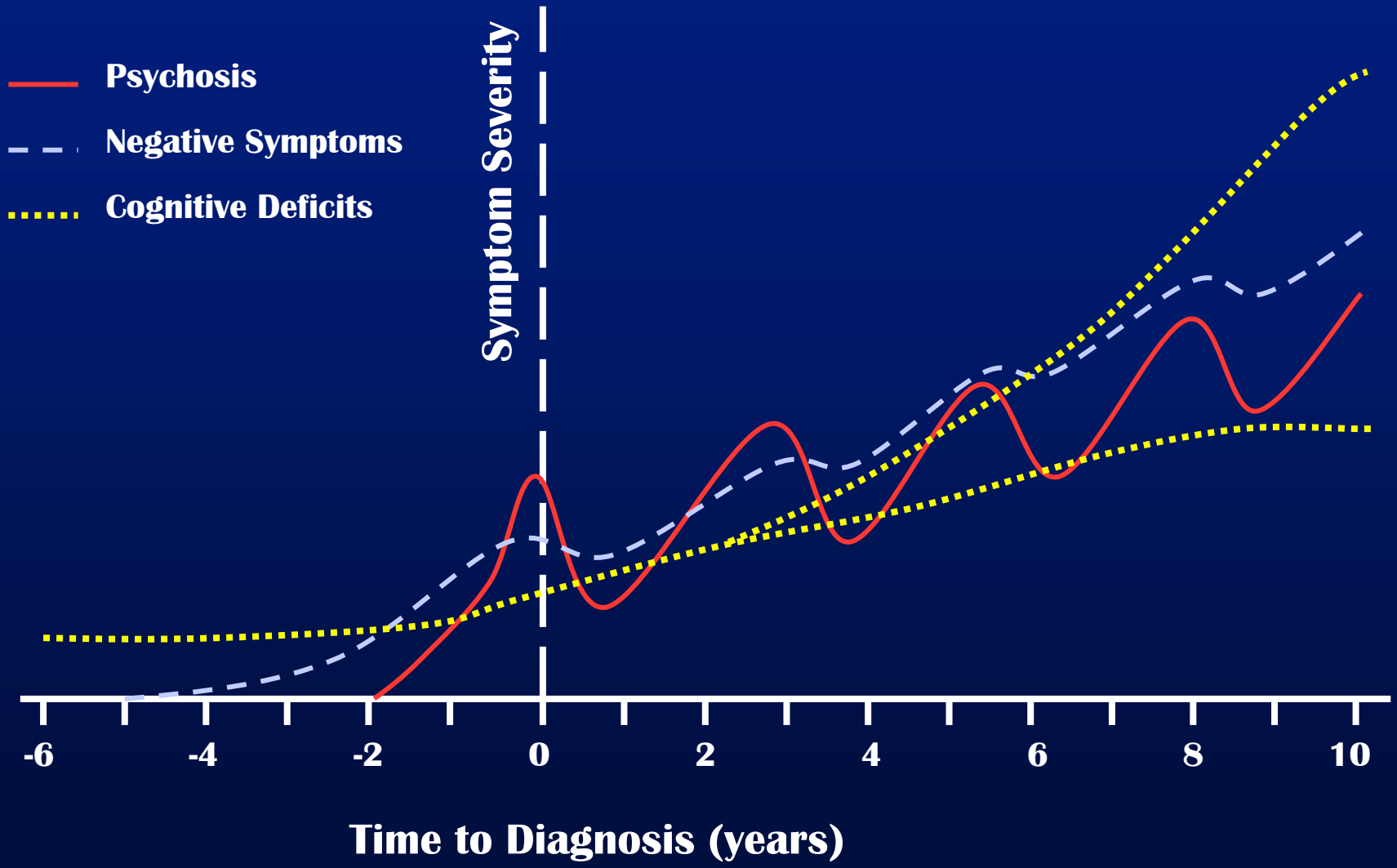
Aims:

- Screen existing recombinant mouse strains (C57Bl BXD) to assess genetic variability in thalamic and hippocampal structure (e.g., volume, cell density)
- Determine whether there are functional correlates of neuroanatomical variability (e.g., performance on tests of memory and sensory filtering)
- Identify genetic loci (RLFPs) linked to such traits
- Determine whether presence of such loci predispose a strain to exaggerated injury following environmental insult (e.g., perinatal administration of kainic acid)

The Mouse Brain Library (www.mbl.org)



Schizophrenia as a Progressive Illness



Clinical Implications of Center Research

- ***Early diagnosis and intervention*** - detecting abnormalities of brain structure during the prodromal phase of schizophrenia

- ***Improved differential diagnosis*** - detecting abnormalities of brain structure present in patients with schizophrenia but not in patients with closely similar illnesses (e.g., bipolar disorder)

- ***Development of new treatments*** - improving our understanding of the pathogenesis during its early phase, and developing new drug therapies or other treatments based on that understanding

How You Can Help?

- ***Subject Referral*** - patients with schizophrenia who have well siblings in the age range of 14-26

- ***Contact Information*** - Please call our administrative office at 314-747-2160, or e-mail us at joann@conte.wustl.edu

- ***Visit our website*** - htttp://www.conte.wustl.edu